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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,300	02/15/2006	Reimo Tetzner	82508	7918
23685 7590 09/05/2008 KRIEGSMAN & KRIEGSMAN 30 TURNPIKE ROAD, SUITE 9 SOUTHBOROUGH, MA 01772			EXAMINER SALMON, KATHERINE D	
			ART UNIT 1634	PAPER NUMBER
			MAIL DATE 09/05/2008	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/568,300

**Applicant(s)**

TETZNER ET AL.

**Examiner**

KATHERINE SALMON

**Art Unit**

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 June 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-28 and 31 is/are pending in the application.
- 4a) Of the above claim(s) 31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/CDC)
- Paper No(s)/Mail Date \_\_\_\_\_

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

1. This action is in response to papers filed. Currently Claims 1-28 and 31 are pending. Claims 29-30 have been cancelled.
2. Claim 31 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/10/2008 and it has been made FINAL.
3. This application contains claim 31 drawn to an invention nonelected with traverse in the reply filed on 9/10/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
4. The following rejections for claims 1-28 are reiterated. Response to arguments follows.
5. This action is FINAL.

***Withdrawn Rejections***

6. The rejection of the claims made under 35 USC 112/2nd paragraph made in section 4 of the previous office action is moot based upon the amendments to the claims.
7. The rejection of the claims made under 35 103(a) made in sections 8-9 in the previous office action over Distler et al. in view of Solinas et al. have been withdrawn. Specifically the PCT application used for the 102(e) date was not filed in English and

therefore priority can not be given to the filing date of the PCT for use as an art date reference.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2 and 4-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eads et al. (Nucleic acids Research 2000 Vol. 28 p. e32) in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96).

Eads et al. teaches a method for detecting of cytosine methylation (abstract).

With regard to Claim 1 step a, Eads et al. teaches reacting the DNA with a chemical (e.g. sodium bisulfite) to change unmethylated cytosine to uracil (p. ii 1<sup>st</sup> column last full sentence). With regard to Claim 1 step b, Eads et al. teaches PCR amplification with a polymerase, at least one primer, and a probe (p. ii 2<sup>nd</sup> column Methylight primer and probe sequences and Figure 1). However, Eads et al. does not teaches that the primer is joined with a probe via a linker. With regard to Claim 1 step c-e, Eads et al. teaches separating the primer strand and detection whether or not hybridization of the probe has occurred (figure 1).

With regard to Claim 2, Eads et al. teaches reacting the DNA with sodium bisulfite (p. ii 1<sup>st</sup> column last full sentence).

With regard to Claims 4-5, Eads et al. teaches a method of MSP RT-PCR (p. ii 1<sup>st</sup> column last paragraph and 2<sup>nd</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 6, Eads et al. teaches a probe that has two signal components that are proximity to one another (p. ii 2<sup>nd</sup> column 2<sup>nd</sup> paragraph).

With regard to Claim 7, Eads et al. teaches quencher-florescent dye pair (p. ii 2<sup>nd</sup> column 2<sup>nd</sup> paragraph).

With regard to Claim 17, Eads et al. teaches that several sequences are simultaneously amplified (p. ii 2<sup>nd</sup> column 2<sup>nd</sup> and 3<sup>rd</sup> paragraphs).

With regard to Claim 29, Eads et al teaches a method of using for diagnosing mismatching in genes associated with cancer disorders (abstract).

However, Eads et al. does not teaches that the primer is joined with a probe via a linker.

Solinas et al. teaches using Scorpion primers in PCR assays (abstract). With regard to Claim 1, Solinas et al. teaches a primer whose 5' end is joined with a probe via a linker (e.g. Scorpion primer) (Figure 1).

With regard to Claim 8, Solinas et al. teaches the probe forms a hairpin shape (p. 1<sup>2nd</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 9, Solinas et al. teaches the probe bears two signal components separated in the inactive form and activated after hybridization (Figure 1A).

With regard to Claim 10, Solinas et al. teaches detecting the signal using FRET (p. 3<sup>1st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 11, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide (Figure 1B).

With regard to Claim 12, Solinas et al. teaches detecting the signal using FRET (p. 3<sup>1st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 13, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide thereby separating the signals in the inactive form (Figure 1B).

With regard to Claim 14, Solinas et al. teaches a method wherein the probe comprises a signal and the other oligonucleotide bears a signal and under hybridization there is a signal (Figure 1b).

With regard to Claim 15, Solinas et al. teaches detecting the signal using FRET (p. 3<sup>1st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 16 Solinas et al. teaches another binder binds in immediate proximity to the probe (Figure 1B).

With regard to Claim 18, Solinas et al. teaches that two scorpion primers can be used (Table 2).

With regard to Claim 19, Solinas et al. teaches that each Scorpion primer has a different signal (Table 2).

With regard to Claims 20, 21, and 28, Solinas et al. teaches Scorpion primers can be used to detect differences in nucleic acid structure (abstract). It would be obvious to design Scorpion primers to detect methylation and nonmethylated areas of the nucleic acid to use the primers in the methylation assay of Eads et al. Eads et al. teaches designing probes which hybridize to methylated and nonmethylated nucleic acid structures (Figure 1 of Eads et al.).

With regard to Claims 22-24, Solinas et al. teaches a probe with a quencher and a dye molecule which are in the inactive form when in spatial proximity (e.g. hairpin form) and are activated by hybridization of the probe to a primer extension product (Figure 1A).

With regard to Claims 25-27, Solinas et al teaches an assay wherein the probe comprises a dye molecular and another oligonucleotides comprises a quencher and when the two are close they are inactive but after hybridization they are active (e.g. a duplex) (Figure 1B).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of Eads et al. to include Scorpion primers linked to

probes as taught by Solinas et al. The ordinary artisan would be motivated to modify the methylation method of Eads et al. to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a very fast and reliable detection system (p. 1 2<sup>nd</sup> column 2<sup>nd</sup> paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably.

### **Response to Arguments**

The reply traverses the rejection. A summary of the arguments presented in the reply is provided below with a response to arguments following.

The reply asserts that Scorpion primers of Solinas et al. are only used for genomic DNA for the analysis of SNPs or mutations whereas the primers of Eads et al. are used in methylation analysis (p. 19 last paragraph). The reply provides an analysis of the method steps involved in bisulfite treatment (p. 129 last paragraph and p. 20 1st paragraph). The reply asserts that due to chemical and physical differences between genomic DNA and bisulfite-treated DNA one would not have used Scorpion primers used in connection to genomic DNA to use with sulfite-treated DNA. The reply points to several advantages of using Scorpion primers (p. 21 1st paragraph).

The arguments presented in the reply have been fully reviewed but have not been found persuasive.

The reply asserts that the combination of using scorpion primers in a methylation

technique is not obvious. It is noted that the argument there are fundamental differences between bisulfite DNA and genomic DNA which has not been pointed out in a particular reference or by a declaration of one skilled in the art and therefore the Attorney's arguments cannot take the place of evidence on the record. As stated in the MPEP, 2106 "Arguments of Counsel"

"However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. *In re Rothermel*, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

- (1) prior to a final rejection,
- (2) before appeal in an application not having a final rejection, or
- (3) after final rejection and submitted
  - (i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
  - (ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
  - (iii) under 37 CFR 1.129(a).

However, with regard to the assertion that the skilled artisan would not use Scorpion primers in a bisulfite treated DNA assay has been reviewed but have not been found y

persuasive. Solinas et al. teaches using scorpion primers in a PCR assay to detect mutations in target samples

Specifically the reply asserts that the genomic DNA of Solinas et al. differs chemically and physically from the bisulfite-treated DNA of Eads et al. in and that the bisulfite treated DNA is strongly fragmented and therefore has a large amount of false positive signals. Grunau et al. (Nucleic Acids Research 2001 Vol. 29 p. e65) teaches the basic protocol for using bisulfite treated DNA in a PCR assay (p. 3 1<sup>st</sup> paragraph). Grunau et al. teaches that optimization parameters and incubation times must be determined to determine the DNA degradation during bisulfite treatment, however, PCR products can be generated (abstract). Therefore Grunau et al. teaches that although bisulfite treated DNA is fragmented PCR amplification can be preformed.

Further, the ordinary artisan would be motivated to look for mutations or changes between two targets of bisulfite-treated DNA to make an assertion of a population. There has been no evidence presented that bisulfite treated DNA reacts differently to genomic DNA with regard to the use of Scorpion primers and therefore it would be obvious to use Scorpion primers with any form of DNA including bisulfite treated DNA.

The reply asserts that bisulfite treated DNA contains bases that are not present in DNA, that bisulfite treated DNA consists of large stretches of three bases, that bisulfite treated DNA is single stranded (p. 20 1-3rd paragraphs). However, the art teaches that although genomic and bisulfite DNA has these physical differences, both of these targets can be used in a PCR assay with optimization. As taught by Grunau et al.

bisulfite treated DNA requires optimization parameters and incubation times to be determined, however, PCR products can be generated from bisulfite treated DNA.

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eads et al. (Nucleic acids Research 2000 Vol. 28 p. e32) in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96) as applied to Claims 1-2 and 4-28 and in further view of Berlin et al. (US Patent Application Publication 2006/0183128 August 17, 2006).

The combination of Eads et al. and Solinas et al. teaches a method for detection of cytosine methylations in DNA, however, Eads et al. and Solinas et al. do not teach the addition of cytidine deaminase.

Berlin et al. teaches a method of DNA methylation. With regard to Claim 3, Berlin et al. teaches cytidine deaminase to use in methylation reaction (paragraph 166 p 17).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of Eads et al. and Solinas et al. to include the reaction of cytidine deaminase as taught by Berlin et al. The ordinary artisan would be motivated to modify the methylation method of Eads et al. and Solinas et al. to include a reaction step with cytidine deaminase because Berlin et al. teaches that cytidine deaminase will convert cytosine bases which are unmethylated at the 5' position to uracil to differentiate between methylated and unmethylated cytosine bases (paragraph 166 p. 17). The ordinary artisan would be motivated to treat the DNA with cytidine

deaminase such that there is a detectable difference between methylated and unmethylated cytosine bases.

### **Response to Arguments**

The reply traverses the rejection. A summary of the arguments presented in the reply is provided below with a response to arguments following.

The reply asserts that the combination of Eads et al. and Solinas et al. is not obvious in view of using Scorpion primers in a bisulfite treated assay (p. 22 last full paragraph).

The arguments presented in the reply have been fully reviewed but have not been found persuasive.

As discussed in the rejection of the claims over Eads et al. and Solinas et al. presented above, the combination of Eads et al and Solinas et al. to make and use the claimed method is obvious in view of the teachings of Solinas et al. which states that Scorpion primers can be used to detect mutations in any sample, and the teachings of Eads et al. which teaches the process of making bisulfite treated DNA.

### ***Double Patenting***

**11.** The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-4, 15-16, 18 of copending Application No. 11716207 in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1,4,5-6 of the instant application is drawn to detecting cytosine methylation in DNA comprising reacting with a chemical or an enzyme, amplifying with a polymerase and at least one primer, separating the extension, and detecting the hybridization. Claim 1-3 and 18 of application no. 11716207 is drawn to

the same method steps however, application 11716207 does not claim that the primer is joined with a probe via a linker.

Claims 2-3 of the instant application and Claim 16 of application no. 11716207 are both drawn to bisulfite reagent.

Claim 7 of the instant application and Claim 15 of application no. 11716207 are drawn to quencher fluorescent dye pairs.

Claim 17 of the instant application and Claim 4 of application no. 11716207 are both drawn to simultaneously amplify.

Application 11716207 does not claim that the primer is joined with a probe via a linker.

Solinas et al. teaches using Scorpion primers in PCR assays (abstract). With regard to Claim 1, Solinas et al. teaches a primer whose 5' end is joined with a probe via a linker (e.g. Scorpion primer) (Figure 1).

With regard to Claim 8, Solinas et al. teaches the probe forms a hairpin shape (p. 1 2<sup>nd</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 9, Solinas et al. teaches the probe bears two signal components separated in the inactive form and activated after hybridization (Figure 1A).

With regard to Claim 10, Solinas et al. teaches detecting the signal using FRET (p. 3 1<sup>st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 11, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide (Figure 1B).

With regard to Claim 12, Solinas et al. teaches detecting the signal using FRET (p. 3 1<sup>st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 13, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide thereby separating the signals in the inactive form (Figure 1B).

With regard to Claim 14, Solinas et al. teaches a method wherein the probe comprises a signal and the other oligonucleotide bears a signal and under hybridization there is a signal (Figure 1b).

With regard to Claim 15, Solinas et al. teaches detecting the signal using FRET (p. 3 1<sup>st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 16 Solinas et al. teaches another binder binds in immediate proximity to the probe (Figure 1B).

With regard to Claim 18, Solinas et al. teaches that two scorpion primers can be used (Table 2).

With regard to Claim 19, Solinas et al. teaches that each Scorpion primer has a different signal (Table 2).

With regard to Claims 20, 21, and 28, Solinas et al. teaches Scorpion primers can be used to detect differences in nucleic acid structure (abstract). It would be obvious to design Scorpion primers to detect methylation and nonmethylated areas of the nucleic acid to use the primers in the methylation assay of Eads et al. Eads et al. teaches designing probes which hybridize to methylated and nonmethylated nucleic acid structures (Figure 1 of Eads et al.).

With regard to Claims 22-24, Solinas et al. teaches a probe with a quencher and a dye molecule which are in the inactive form when in spatial proximity (e.g. hairpin form) and are activated by hybridization of the probe to a primer extension product (Figure 1A).

With regard to Claims 25-27, Solinas et al teaches an assay wherein the probe comprises a dye molecular and another oligonucleotides comprises a quencher and when the two are close they are inactive but after hybridization they are active (e.g. a duplex) (Figure 1B).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of application 11716207 to include Scorpion primers linked to probes as taught by Solinas et al. The ordinary artisan would be motivated to modify the methylation method of application 11716207 to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a very fast and reliable detection system (p. 1 2<sup>nd</sup> column 2<sup>nd</sup> paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably.

Accordingly, the claims of application 11716207 and the claims of the instant application are coextensive in scope and not patentably distinct form each other.

This is a provisional obviousness-type double patenting rejection.

**Response to arguments**

The reply traverses the rejection. A summary of the arguments presented in the reply is summarized below with response to arguments following.

The applicant requests that the double patenting rejection be held in abeyance until the allowance of the claims (p. 27 last paragraph).

The rejection will be maintained.

13. Claims 1-2, 4-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-2,11,14,18-19, and 27 of copending Application No. 10482433 in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96).

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1,4,5-6 of the instant application is drawn to detecting cytosine methylation in DNA comprising reacting with a chemical or an enzyme, amplifying with a polymerase and at least one primer, separating the extension, and detecting the hybridization. Claim 1-2, 27 of application no. 10482433 is drawn to the same method steps however, application 10482433 does not claim that the primer is joined with a probe via a linker.

Claims 2 of the instant application and Claim 11 of application no. 10482433 are both drawn to bisulfite reagent.

Claim 7 of the instant application and Claim 18-19 of application no. 10482433

are drawn to quencher fluorescent dye pairs.

Claim 17 of the instant application and Claim 14 of application no. 10482433 are both drawn to simultaneously amplify.

Application 10482433 does not claim that the primer is joined with a probe via a linker.

Solinas et al. teaches using Scorpion primers in PCR assays (abstract). With regard to Claim 1, Solinas et al. teaches a primer whose 5' end is joined with a probe via a linker (e.g. Scorpion primer) (Figure 1).

With regard to Claim 8, Solinas et al. teaches the probe forms a hairpin shape (p. 1 2<sup>nd</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 9, Solinas et al. teaches the probe bears two signal components separated in the inactive form and activated after hybridization (Figure 1A).

With regard to Claim 10, Solinas et al. teaches detecting the signal using FRET (p. 3 1<sup>st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 11, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide (Figure 1B).

With regard to Claim 12, Solinas et al. teaches detecting the signal using FRET (p. 3 1<sup>st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 13, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide thereby separating the signals in the inactive form (Figure 1B).

With regard to Claim 14, Solinas et al. teaches a method wherein the probe comprises a signal and the other oligonucleotide bears a signal and under hybridization there is a signal (Figure 1b).

With regard to Claim 15, Solinas et al. teaches detecting the signal using FRET (p. 3 1<sup>st</sup> column 1<sup>st</sup> paragraph).

With regard to Claim 16 Solinas et al. teaches another binder binds in immediate proximity to the probe (Figure 1B).

With regard to Claim 18, Solinas et al. teaches that two scorpion primers can be used (Table 2).

With regard to Claim 19, Solinas et al. teaches that each Scorpion primer has a different signal (Table 2).

With regard to Claims 20, 21, and 28, Solinas et al. teaches Scorpion primers can be used to detect differences in nucleic acid structure (abstract). It would be obvious to design Scorpion primers to detect methylation and nonmethylated areas of the nucleic acid to use the primers in the methylation assay of Eads et al. Eads et al. teaches designing probes which hybridize to methylated and nonmethylated nucleic acid structures (Figure 1 of Eads et al.).

With regard to Claims 22-24, Solinas et al. teaches a probe with a quencher and a dye molecule which are in the inactive form when in spatial proximity (e.g. hairpin form) and are activated by hybridization of the probe to a primer extension product (Figure 1A).

With regard to Claims 25-27, Solinas et al teaches an assay wherein the probe comprises a dye molecular and another oligonucleotides comprises a quencher and when the two are close they are inactive but after hybridization they are active (e.g. a duplex) (Figure 1B).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of application 10482433 to include Scorpion primers linked to probes as taught by Solinas et al. The ordinary artisan would be motivated to modify the methylation method of application 10482433 to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a very fast and reliable detection system (p. 1 2<sup>nd</sup> column 2<sup>nd</sup> paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably.

Accordingly, the claims of application 10482433 and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection.

#### **Response to arguments**

The reply traverses the rejection. A summary of the arguments presented in the reply is summarized below with response to arguments following.

The applicant requests that the double patenting rejection be held in abeyance until the allowance of the claims (p. 27 last paragraph).

The rejection will be maintained until the applicant presents persuasive arguments that the applications are not obvious double patent applications, a terminal disclaimer is filed, or the claim are amended to sufficiently overcome the rejection.

### ***Conclusion***

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**15.** Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/  
Examiner, Art Unit 1634

/Ram R. Shukla/  
Supervisory Patent Examiner, Art Unit 1634